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Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional specification filed on 12/08/2003 in respect of Patent Application No.792/MUM/2003 of Cadila Healthcare Limited, a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

Dated this 2nd day of April 2004

(R.BHATTACHARYA)
ASST. CONTROLLER OF PATENTS & DESIGNS.

FORM 1

THE PATENTS ACT, 1970

APPLICATION FOR GRANT OF PATENT
(See Sections 5(2), 7, 54 and 135 and Rule 33A)

(1) We, **CADILA HEALTHCARE LIMITED,** a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India

(2) hereby declare –

(a) That we are in possession of an invention titled

'Novel heterocyclic compounds having hypolipidemic, hypocholesteremic activities, process for their preparation and pharmaceutical compositions containing them and their use in medicine'

(b) That the Provisional Specification relating to this invention is filed with this application;

(c) That there is no lawful ground of objection to the grant of a patent to us.

(3) Further declare that the true and first inventor for the said invention are ,

Braj Bhushan LOHRAY and Vidya Bhushan LOHRAY both Indian citizens, of CADILA HEALTHCARE LIMITED, Zydus Towers, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India

(4) We claim priority from the application(s) filed in the following convention country(ies), particulars of which are as follows: **NIL**

(5) That we are the assignees of the true and first inventors,

(6) That our address for service in India is as follows;

M/s Subramaniam, Natraj & Associates
Attorneys-At-Law
E-556, Greater Kailash-II
New Delhi - 110 048, India.

Phone: +91 11 29215603, 29226012, 29216025
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Email: sna@vsnl.com

792/MUM/2003
12/8/2003

Received Rs. 3000/- in Cash
Cheque/M.O./P.O. on 12/8/03
Vide Entry No. 4314 in the Register of Valuables, Bombay.
12-8-03

(7) Following declarati[redacted]as given by the inventors -

We, **Braj Bhushan LOHRAY and Vidya Bhushan LOHRAY,** both Indian citizens, of CADILA HEALTHCARE LIMITED, Zydus Towers, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India,

and the true and first inventors for this invention declare that the applicants herein is our assignees.

Braj Bhushan LOHRAY **Vidya Bhushan LOHRAY**

(8) That to the best of our knowledge, information and belief the facts and matters stated herein are correct and there is no lawful ground of objection to the grant of patent to us on this application.

(9) Following are the attachments with this application:
(a) Provisional specification in triplicate
(b) Statement and Undertaking on FORM 3 in duplicate
(c) Power of Authority
(d) Form 2 in triplicate
(e) Power of Authority
(f) Abstract

Fee Rs. ..... in Cash/Cheque/Bank Draft Bearing No..... dated.....on .....Bank.

We request that a patent be granted to us on any complete specification filed on this application for the said invention.

Dated this 11th day of August, 2003.

(Dr. Braj Bhushan Lohray, President, Zydus Research Centre)
for CADILA HEALTHCARE LIMITED

To
The Controller of Patents
The Patent Office, at Mumbai

FORM 2

The PATENT ACT, 1970
(39 of 1970)
Provisional Specification

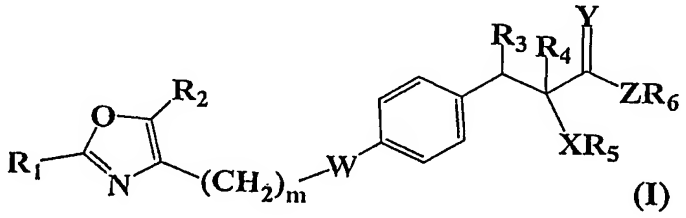
NOVEL HETEROCYCLIC COMPOUNDS HAVING HYPOLIPIDEMIC, HYPOCHOLESTEREMIC ACTIVITIES PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE IN MEDICINE

CADILA HEALTH CARE LTD, Zydus Research Centre
Zydus Tower, Satellite Cross Road, Sarkhej-Gandhinagar Highway,
Ahmedabad-380015, Gujarat, India

The following specification describes the nature of the invention and the manner in which it is to be performed:

FIELD OF INVENTION

The present invention relates to novel hypolipidaemic and hypocholesterolemic compounds, their derivatives, their analogs, their tautomeric forms, their pharmaceutically acceptable salts, and pharmaceutically acceptable compositions containing them. More particularly, the present invention relates to novel oxazol derivatives of the general formula (I), their derivatives, their analogs, their tautomeric forms, their pharmaceutically acceptable salts, pharmaceutical compositions containing them, use of these compounds in medicine and the intermediates involved in their preparation.



(I)

The present invention also relates to a process for the preparation of the above said novel compounds, their derivatives, their analogs, their tautomeric forms, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them.

The compounds of the general formula (I) lower or modulate triglyceride levels and/or cholesterol levels and/or low-density lipoproteins (LDL) and raise HDL plasma levels and hence are useful in combating different medical conditions, where such lowering (and raising) is beneficial. Thus, it could be used in the treatment and/or prophylaxis of obesity, hyperlipidaemia, hypercholesteremia, hypertension, atherosclerotic disease events, vascular restenosis, diabetes and many other related conditions.

The compounds of general formula (I) are useful to prevent or reduce the risk of developing atherosclerosis, which leads to diseases and conditions such as artereosclerotic cardiovascular diseases, stroke, coronary heart diseases, cerebrovascular diseases, peripheral vessel diseases and related disorders.

These compounds of general formula (I) are useful for the treatment and/or prophylaxis of metabolic disorders loosely defined as Syndrome X. The characteristic features of Syndrome X include initial insulin resistance followed by hyperinsulinemia, dyslipidemia and impaired glucose tolerance. The glucose intolerance can lead to non-insulin dependent diabetes mellitus (NIDDM, Type 2 diabetes), which is characterized by hyperglycemia, which if not controlled may lead to diabetic complications or metabolic disorders caused by insulin resistance. Diabetes is no longer considered to be associated only with glucose metabolism, but it affects anatomical and physiological parameters, the intensity of which vary depending upon stages/duration and severity of the diabetic state. The compounds of this invention are also useful in prevention, halting or slowing progression or reducing the risk of the above mentioned disorders along with the resulting secondary diseases such as cardiovascular diseases, like arteriosclerosis, atherosclerosis; diabetic retinopathy, diabetic neuropathy and renal disease including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal diseases, like microalbuminuria and albuminuria, which may be result of hyperglycemia or hyperinsulinemia.

The compounds of the present invention can be useful as aldose reductase inhibitors; for improving cognitive functions in dementia, and in the treatment and/or prophylaxis of disorders such as psoriasis, polycystic ovarian syndrome (PCOS), cancer, osteoporosis, leptin resistance, inflammation and inflammatory bowel diseases, xanthoma, pancreatitis, myotonic dystrophy, endothelial cell dysfunction and hyperlipidemia.

The compounds of the present invention are useful in the treatment of the diseases mentioned herein, alone or in combination one or more hypoglycemic, antihyperglycemic, hypolipidaemic, hypolipoproteinemic agents, antioxidants, antihypertensives, such as HMG CoA reductase inhibitor, fibrate, statins, glitazones, sulfonyl ureas, insulin, α-glycosidase inhibitors, nicotinic acid, cholestyramine, cholestipol or probucol, and the like.

BACKGROUND OF THE INVENTION

Hyperlipidaemia has been recognized as the major risk factor in causing cardiovascular diseases due to atherosclerosis. Atherosclerosis and other such peripheral vascular diseases affect the quality of life of a large population in the world. The therapy aims to lower the elevated plasma LDL cholesterol, low-density lipoprotein and plasma triglycerides in order to prevent or reduce the risk of occurrence of cardiovascular diseases. The detailed etiology of atherosclerosis and coronary artery diseases is discussed by Ross and Glomset [New Engl. J. Med., 295, 369-377 (1976)].

Diabetes is associated with a number of complications and also affect a large population. This disease is usually associated with other diseases such as obesity, hyperlipidemia, hypertension and angina. It is well established that improper treatment can aggravate impaired glucose tolerance and insulin resistance, thereby leading to frank diabetes. Further, patients with insulin resistance and type 2 diabetes often have raised triglycerides and low HDL-cholesterol concentrations and therefore, have greater risk of cardiovascular diseases. The present therapy for these diseases includes sulfonylureas and biguanides along with insulin. This type of drug therapy may lead to mild to severe hypoglycemia, which may lead to coma or in some cases may lead to death, as a result of unsatisfactory glycaemic control by these drugs. Recent addition of drugs in the treatment of diabetes are the thiazolidinediones, drugs having insulin-sensitizing action. Thiazolidinediones are prescribed alone or in combination with other anti-diabetic agents like

troglitazone, rosiglitazone and pioglitazone. These are useful in treating diabetes, lipid metabolism but are suspected to have tumor-inducing potential and cause hepatic dysfunction, which may lead to liver failure. Further, serious undesirable side-effects have occurred in animal and/or human studies which include cardiac hypertrophy, hema dilution and liver toxicity in a few glitazones progressing to advanced human trials. The drawback is considered to be idiosyncratic. Presently, there is a need for a safe and an effective drug, to treat insulin resistance, diabetes and hyperlipidemia.[*Exp. Clin. Endocrinol. Diabetes*: 109(4), S548-9 (2001)]

Obesity is another major health problem being associated with increased morbidity and mortality. It is a metabolic disorder, in which excess of fat is accumulated in the body. Although, its etiology is unclear, the general feature includes excess of calorie intake than it is consumed. Various therapies such as dieting, exercise, appetite suppression, inhibition of fat absorption etc. have been used to combat obesity. However, more efficient therapies to treat this abnormality is essential as obesity is closely related to several diseases such as coronary heart disease, stroke, diabetes, gout, osteoarthritis, hyperlipidaemia and reduced fertility. It also leads to social and psychological problems.[*Nature Reviews: Drug Discovery* : 1(4), 276-86 (2002)]

Peroxisome Proliferator Activated Receptor (PPAR) is a member of the steroid/ retinoid/ thyroid hormone receptor family. PPARα, PPARγ and PPARδ have been identified as subtypes of PPARs. The role of PPAR, in different disease conditions is widely established PPARγ activation has been found to play a central role in initiating and regulating adipocyte differentiation [Endocrinology 135, 798-800, (1994)] and energy homeostasis, [*Cell*, 83, 803-812 (1995); *Cell*, 99, 239-242 (1999)]. PPARγ agonists would stimulate the terminal differentiation of adipocyte precursors and cause morphological and molecular changes characteristic of a more differentiated, less malignant state. During adipocyte differentiation, several highly specialized proteins are induced, which are being involved in lipid storage

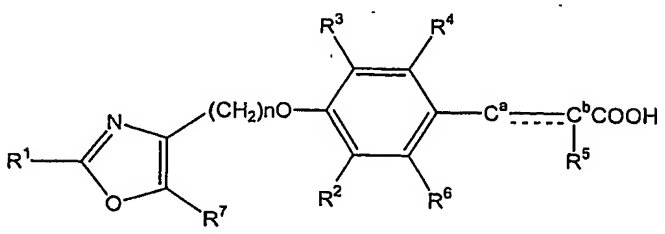
and metabolism. It is accepted that PPARγ activation leads to expression of CAP gene [Cell biology, 95, 14751-14756, (1998)], however, the exact link from PPARγ activation to changes in glucose metabolism and decrease in insulin resistance in muscle has not been clear. PPARα is involved in stimulating β-oxidation of fatty acids [*Trends Endocrine. Metabolism*, 4, 291-296 (1993)] resulting in plasma circulating free fatty acid reduction [*Current Biol.*, 5, 618-621 (1995)]. Recently, role of PPARγ activation in the terminal differentiation of adipocyte precursors has been implicated in the treatment of cancer. [*Cell*, 79, 1147-1156 (1994); *Cell*, 377-389 (1996); *Molecular Cell*, 465-470 (1998); *Carcinogenesis*, 1949-1953 (1998); *Proc. Natl. Acad. Sci.*, 94, 237-241 (1997); *Cancer Research*, 58, 3344-3352 (1998)]. Since PPARγ is expressed in certain cells consistently, PPARγ agonists would lead to nontoxic chemotherapy. There is growing evidence that PPAR agonists may also influence the cardiovascular system through PPAR receptors as well as directly by modulating vessel wall function [*Med. Res. Rev.*, 20 (5), 350-366 (2000)].

PPAR α agonists have been found useful in the treatment of obesity (WO 97/36579). Dual PPAR α and γ agonists have been suggested to be useful for Syndrome X (WO 97/25042). PPAR γ agonists and HMG-CoA reductase inhibitors have exhibited synergism and indicated the usefulness of the combination in the treatment of atherosclerosis and xanthoma (EP 0753 298).

Leptin is a protein when bound to leptin receptors is involved in sending satiety signal to the hypothalamus. Leptin resistance would therefore lead to excess food in-take, reduced energy expenditure, obesity, impaired glucose tolerance and diabetes [*Science*, 269, 543-46(1995)]. It has been reported that insulin sensitizers lower plasma leptin concentration [*Proc. Natl. Acad. Sci.* 93, 5793-5796 (1996): WO 98/02159)].

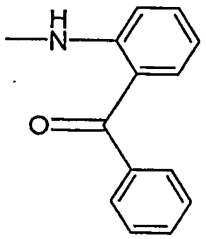
A number of compounds belonging to the class of oxazole derivatives have been reported to be useful in the treatment of hyperlipidemia, hypercholesterolemia and hyperglycemia which includes

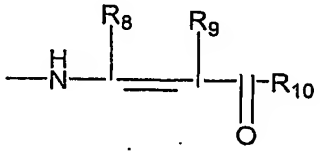
WO 02092084 (Hoffmann La Roche) describes oxazole compounds having the following general formula



wherein, R^1 is aryl or heteroaryl;

R^2, R^3, R^4 and R^5 are independently selected from the group consisting of hydrogen, hydroxy, lower-alkenyl, halogen, lower-alkyl and lower-alkoxy, wherein at least one of R^2, R^3, R^4 and R^6 is not hydrogen, or R^3 and R^4 are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R^3 and R^4 together are -CH=CH-S-, -S-CH=CH-, -CH=CH-O-, -O-CH=CH-, -CH=CH-CH=CH-, $-(CH_2)_{3-5}-$, $-O-(CH_2)_{2-3}-$ or $-(CH_2)_{2-3}-O-$; R^5 is lower-alkoxy, lower-alkenyloxy, or

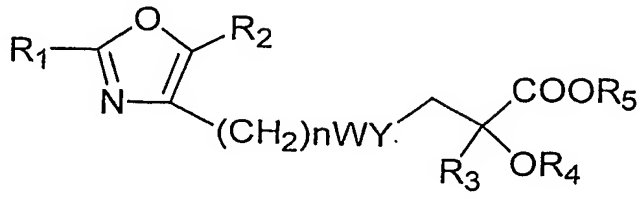




or

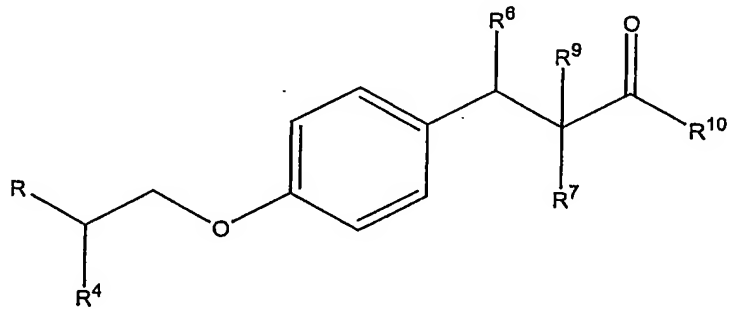
R^7, R^8, R^9, each represent H or lower-alkyl; R^{10} is aryl; n is 1, 2 or 3; the bond between C_a & C_b represent a carbon-carbon single or double bond;

WO 0216331(Eli Lilly & Co.) discloses oxazolyl-arylpropionic acid derivatives of the following general formula

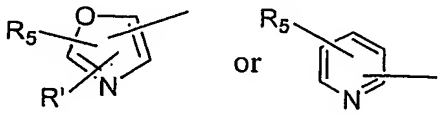


where R_1 is substituted or unsubstituted groups selected from aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, $(CH_3)_3C$-; n = 2, 3, 4; W represents CH_2, CH(OH), CO, O; R_2 represents H, alkyl, haloalkyl, C_6H_5; Y represents substituted or unsubstituted group consisting of thiophen-2,5-diyl or phenylene; R_3 represents alkyl, haloalkyl; R_4 represents substituted or unsubstituted phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, quinolyl, pyridyl, benzo[1,3]dioxol-5-yl; R_5 represents H, alkyl, aminoalkyl groups.

WO 9807699 (Japan Tobacco, Inc.) describes propionic acid derivative of the following general structure

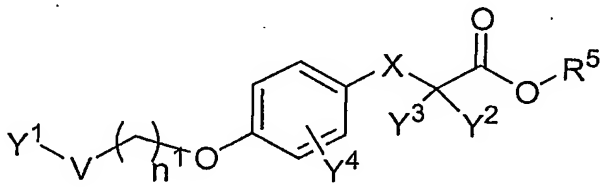


wherein R represents

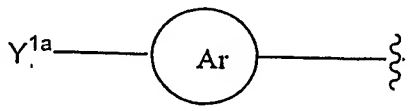


R^1 is an optionally substituted aromatic hydrocarbon, an optionally substituted alicyclic hydrocarbons, an optionally substituted heterocyclic group, or an optionally substituted fused heterocyclic group, R^5 is lower alkyl; R^4 = H or lower alkyl; R^6=H or forms together with R^9, a double bond; R^7 is a carboxy, an acyl, an optionally substituted alkoxycarbonyl, an optionally substituted lower alkyl, an optionally substituted carbamoyl, an optionally substituted aryloxycarbonyl, an optionally substituted aralkyloxycarbonyl or a group of the formula -Y-R^8 wherein Y is -NH- or an oxygen atom and R^8 is an optionally substituted acyl or an optionally substituted alkoxycarbonyl; R^9 = H, an optionally substituted loweralkyl or an optionally substituted alkoxycarbonyl; R^{10} is a hydroxy, an optionally substituted amino, an optionally substituted lower alkoxy, an optionally substituted lower alkyl, an optionally substituted aryloxy or an optionally substituted aralkyloxy, provided that when R^7 is an alkoxycarbonyl and R^9 is a hydrogen atom, R^{10} is not a lower alkoxy.

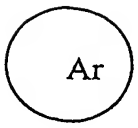
WO 02100403 (Eli Lilly & Co.) discloses compounds of the following general formula suitable for the treatment of Syndrome X



Wherein Y^1 represents

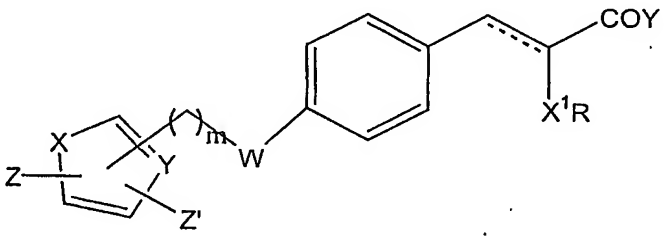


Y^{1a} is H, (C_0-C_3) alkyl-aryl, C(O)-aryl , heteroaryl, cycloalkyl, heterocycloalkyl, aryloxy, etc.;



is aryl or heteroaryl; V is a bond or O; X is CH_2 or O, R^5 is H or C_1-C_6 alkyl; Y^2 and Y^3 are each independently H, C_1-C_6 alkyl or C_1-C_6 alkoxy; Y^4 is (C_1-C_3) alkyl-$NR^5C(O)$ -(C_0-C_5) alkyl-Y^7 , (C_1-C_3) alkyl-NR^5C O) -(C_2-C_5) alkenyl-Y^7, (C_1-C_3) alkyl-$NR^5C(O)$ -(C_2-C_5) alkynyl-Y^7, CN etc.; Y^7 is H, aryl heteroaryl, C_1-C_{12} alkyl, C_1-C_6 alkoxy, cycloalkyl, heterocycloalkyl, aryloxy, C(O)-heteroaryl etc.; n^1 is 2,3,4 or 5;

US 5232945 (Pfizer Inc.), describes compounds of the following general formula



Wherein Z= H, amino, (C_1-C_7)alkyl, (C_3-C_7)cycloalkyl, phenyl or phenyl mono or disubstituted with (C_1-C_3)alkyl, CF_3, (C_1-C_3)alkoxy, phenyl, phenoxy, benzyl, benzyloxy, fluoro or chloro; Z^1 = H or (C_1-C_3)alkyl; R = (un)substituted alkyl, cycloalkyl, alkenyl, alkynyl, Ph, phenylalkyl, alkanoyl; X = S, O, NR_2, -CH=CH, -CH=N, -N=CH; R_2 = H, alkyl, Ph, CH_2Ph; Y = CH, N; X^1 = O, S, SO, SO_2; Y^1 = OH, (un)substituted alkoxy, OPh, OCH_2Ph, NH_2 etc.; W = O, CO, CH_2, CH(OH), -CH=CH; m = 0, 1, 2;

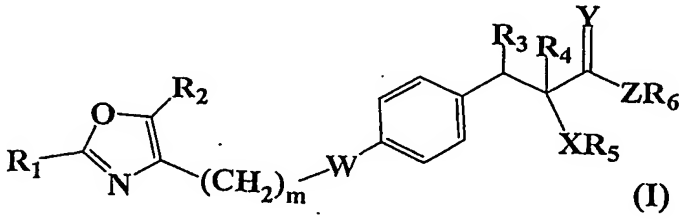
Several other oxazole derivatives useful in the treatment of diabetes, hyperlipidemia etc. (Syndrome X) have been reported for e.g. WO 0320269, WO 0216332, WO 0218355, WO 0216331, WO 0216332, WO 0296895, WO 0296895, WO 0296894, WO 0296893, WO 0262774, WO 0250048, WO 0250047, WO 0276957, WO 0251820, WO 0214291, WO 0138325, WO 0116120, WO 0100403, WO 0116111, WO 0116120, WO 0179202, WO 0179197, WO 0008002, US 20010008898, JP 2002338555, JP 2001261612 which are incorporated in their entirety as reference.

However, none of them have been commercialized so far and there is always a need to provide better and cost effective medicines which are of better or comparable efficacy

with the present treatment regimes, has lesser side effects and requires a lower dosage regime.

SUMMARY OF THE INVENTION

The present invention thus provides for new compounds of general formula (I)



(I)

their derivatives, their analogs, their tautomeric forms, their pharmaceutically acceptable salts, and pharmaceutically acceptable compositions containing them and their use in medicine. The present invention also discloses a process for the preparation of compounds of formula (I) and pharmaceutical compositions containing them.

OBJECTIVES OF THE INVENTION

The objective of this invention is to develop novel compounds represented by the general formula (I) useful as hypocholesterolemic, hypolipidaemic, hypolipoproteinemic, anti-obesity and antihyperglycemic agents which may have additional body weight lowering effect and beneficial effect in the treatment and/or prophylaxis of diseases caused by hyperlipidaemia, diseases classified under syndrome X and atherosclerosis.

The main objective of the present invention is to provide novel oxazolyl propanoic acid derivatives represented by the general formula (I), their analogs, their tautomeric forms, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them or their mixtures thereof and their use in medicine.

Yet another objective of this invention is to provide processes for the preparation of novel oxazolyl propanoic acids derivatives represented by the general formula (I), their analogs, their tautomeric forms and their pharmaceutically acceptable salts.

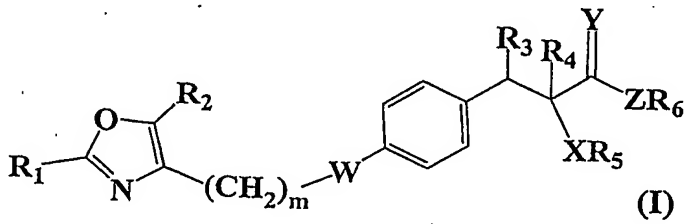
Still another objective of the present invention is to provide pharmaceutical compositions containing compounds of the general formula (I), their analogs, their tautomeric forms, their pharmaceutically acceptable salts or their mixtures in

combination with suitable carriers, solvents, diluents and other media normally employed in preparing such compositions.

A further objective of the present invention is to provide processes for preparation of intermediates involved in the preparation of compounds of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

Accordingly, the present invention relates to compounds of the general formula (I),



(I)

their derivatives, their analogs, their tautomeric forms, their pharmaceutically acceptable salts, wherein

R_1 represents substituted or unsubstituted, single or fused heteroaryl or heterocyclic groups; R_2 represents H, substituted or unsubstituted linear or branched (C_1-C_{12})alkyl group; W represents O, S or NR_7, where R_7 represents hydrogen, (C_1-C_6)alkyl or aryl groups; X represent O or S;

R_3 & R_4 represent hydrogen or together represent a bond; R_5 represents hydrogen, perfluoro(C_1-C_{12})alkyl, substituted or unsubstituted groups selected from linear or branched (C_1-C_{12})alkyl, cyclo(C_1-C_{12})alkyl, aryl, ar(C_1-C_{12})alkyl, heteroaryl, heteroar(C_1-C_{12})alkyl, heterocyclyl, alkoxyalkyl, aryloxyalkyl, alkoxycarbonyl, aryloxycarbonyl, cycloalkyloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl or acyl groups;

Y represents O or S;

Z represents O, S or NR_8 where R_8 represents hydrogen or substituted or unsubstituted groups selected from (C_1-C_{12})alkyl, aryl, ar(C_1-C_{12})alkyl, hydroxy(C_1-C_{12})alkyl, amino(C_1-C_{12})alkyl, heteroaryl or heteroar(C_1-C_{12})alkyl groups;

m represents an integer from 1-4;

R_6 represents hydrogen, substituted or unsubstituted groups selected from linear or branched (C_1-C_{12})alkyl, aryl, ar(C_1-C_{12})alkyl, heteroaryl, heteroar(C_1-C_{12})alkyl, heterocylyl, heterocyclylalkyl, hydroxyalkyl, alkoxyalkyl or alkylaminoalkyl groups;

R_8 and R_6 together may form 5 or 6 membered substituted or unsubstituted heterocyclic ring structure containing one or more heteroatoms selected from O, N or S;

When R_1 is substituted, the substituents may be substituted or unsubstituted groups selected from hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, amidino, guanidino, hydrazino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocylyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylalkoxyacyl, acyl, acyloxy, acylamino, monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, alkylsulfonylamino, alkylsulfonyloxy, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkoxyamino, hydroxyl amino, sulfenyl derivatives, sulfonyl derivatives, sulfonic acid and its derivatives, phosphonic acid and its derivatives.

The various groups, radicals and substituents used anywhere in the specification are described in the following paragraphs.

The term "alkyl" used herein, either alone or in combination with other radicals, denotes a linear or branched radical containing one to twelve carbons, such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, amyl, *t*-amyl, *n*-pentyl , *n*-hexyl, *iso*-hexyl, heptyl, octyl and the like.

The term "alkenyl" used herein, either alone or in combination with other radicals, denotes a linear or branched radical containing one to twelve carbons; such as vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-

hexenyl, 5-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl and the like. The term "alkenyl" includes dienes and trienes of straight and branched chains.

The term "alkynyl" used herein, either alone or in combination with other radicals, denotes a linear or branched radical containing one to twelve carbons, such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, and the like. The term "alkynyl" includes di- and tri-ynes.

The term "cycloalkyl" used herein, either alone or in combination with other radicals, denotes a radical containing three to seven carbons, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

The term "cycloalkenyl" used herein, either alone or in combination with other radicals, denotes a radical containing three to seven carbons, such as cyclopropenyl, 1-cyclobutenyl, 2-cylobutenyl, 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, cycloheptadienyl, cycloheptatrienyl, and the like.

The term "alkoxy" used herein, either alone or in combination with other radicals, denotes a radical alkyl, as defined above, attached directly to an oxygen atom, such as methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, *iso*-butoxy, pentyloxy, hexyloxy, and the like.

The term "alkenoxy" used herein, either alone or in combination with other radicals, denotes an alkenyl radical, as defined above, attached to an oxygen atom, such as vinyloxy, allyloxy, butenoxy, pentenoxy, hexenoxy, and the like.

The term "cycloalkoxy" used herein, either alone or in combination with other radicals, denotes a radical containing three to seven carbon atoms, such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like.

The term "halo" or "halogen" used herein, either alone or in combination with other radicals, such as "haloalkyl", "perhaloalkyl" etc refers to a fluoro, chloro, bromo or iodo group. The term "haloalkyl" denotes a radical alkyl, as defined above, substituted with one or more halogens such as perhaloalkyl, such as fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, trifluoroethyl and the like, mono or polyhalo substituted methyl, ethyl, propyl, butyl, pentyl or hexyl groups. The term "haloalkoxy"

denotes a haloalkyl, as defined above, directly attached to an oxygen atom, such as fluoromethoxy, chloromethoxy, fluoroethoxy chloroethoxy groups, and the like. The term "perhaloalkoxy" denotes a perhaloalkyl radical, as defined above, directly attached to an oxygen atom such as, trifluoromethoxy, trifluoroethoxy, and the like.

The term "aryl" or "aromatic" used herein, either alone or in combination with other radicals, denotes an aromatic system containing one, two or three rings wherein such rings may be attached together in a pendant manner or may be fused, such as phenyl, naphthyl, tetrahydronaphthyl, indane, biphenyl, and the like. The term 'aralkyl" denotes an alkyl group, as defined above, attached to an aryl, such as benzyl, phenethyl, naphthylmethyl, and the like. The term "aryloxy" denotes an aryl radical, as defined above, attached to an alkoxy group, such as phenoxy, naphthyloxy and the like, which may be substituted. The term "aralkoxy" denotes an arylalkyl moiety, as defined above, such as benzyloxy, phenethyloxy, naphthylmethyloxy, phenylpropyloxy, and the like, which may be substituted.

The term "heterocyclyl" or "heterocyclic" used herein, either alone or in combination with other radicals, denotes saturated, partially saturated or unsaturated ring-shaped radicals containing one or more heteroatoms, the heteroatoms being selected from nitrogen, sulfur and oxygen (or oxidised version thereof, such as N-oxide, suphoxide, sulphone). Examples of such heterocyclic radicals include aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, 2-oxopiperidinyl, 4-oxopiperidinyl, 2-oxopiperazinyl, 3-oxopiperazinyl, morpholinyl, thiomorpholinyl, 2-oxomorpholinyl, azepinyl, diazepinyl, oxapinyl, thiazepinyl, oxazolidinyl, thiazolidinyl, dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, quinuclidinyl, tetrahydropyranyl, homopiperazinyl, pyrazolidinyl and the like.

The term "heteroaryl" or "heteroaromatic" used herein, either alone or in combination with other radicals, denotes 5 to 10 membered monocyclic or multicyclic heterocyclic radicals containing one or more hetero atoms selected from O, N or S, attached to an aryl group, such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, tetrazolyl, benzopyranyl, benzothiopyranyl, benzofuranyl, benzothienyl, indolinyl, indolyl, indolizinyl, indazolyl, isoindolyl, azaindolyl, azaindolinyl, quinolinyl, pyrimidinyl, pyrazolyl, pyrrolinyl, quinazolinyl, pyrimidonyl,

benzoxazinyl, benzoxazinonyl, benzothiazinyl, benzothiazinonyl, benzothiadiazolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, thiadiazolyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzotriazolyl imidazo[1,2-a]pyridyl, benzoisoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, isoquinolinyl, phthalazinyl, phthalazinonyl, phenoxazinyl, phenothiazinyl, carbazolyl, benzodioxolyl, benzodioxanyl, tetrazolyl, quinazolinonyl, tetrazolopyridazinyl, and the like.

The term "heterocyclylalkyl" used herein, either alone or in combination with other radicals, represents a heterocyclyl group, as defined above, substituted with an alkyl group of one to twelve carbons, such as pyrrolidinealkyl, piperidinealkyl, morpholinealkyl, thiomorpholinealkyl, oxazolinealkyl, and the like, which may be substituted. The term "heteroaralkyl" used herein, either alone or in combination with other radicals, denotes a heteroaryl group, as defined above, attached to a straight or branched saturated carbon chain containing 1 to 6 carbons, such as (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl and the like. The terms "heteroaryloxy", "heteroaralkoxy", "heterocycloxy", "heterocylylalkoxy" denotes heteroaryl, heteroarylalkyl, heterocyclyl, heterocylylalkyl groups respectively, as defined above, attached to an oxygen atom.

The term "acyl" used herein, either alone or in combination with other radicals, denotes a radical containing one to eight carbons such as formyl, acetyl, propanoyl, butanoyl, *iso*-butanoyl, pentanoyl, hexanoyl, heptanoyl, benzoyl and the like, the aryl groups may be substituted.

The term "acyloxy" used herein, either alone or in combination with other radicals, denotes a radical acyl, as defined above, directly attached to an oxygen atom, such as acetyloxy, propionyloxy, butanoyloxy, *iso*-butanoyloxy, benzoyloxy and the like and may be substituted.

The term "acylamino" used herein, either alone or in combination with other radicals, denotes an acyl group as defined earlier attached to one amino group and may be CH_3CONH, C_2H_5CONH, C_3H_7CONH, C_4H_9CONH, C_6H_5CONH and the like, which may be substituted.

The term "mono-substituted amino" used herein, either alone or in combination with other radicals, denotes an amino group, substituted with one group selected from (C_1-C_6)alkyl, substituted alkyl, aryl, substituted aryl or arylalkyl groups. Examples of monoalkylamino group include methylamine, ethylamine, *n*-propylamine, *n*-butylamine, *n*-pentylamine and the like and may be substituted.

The term 'disubstituted amino" used herein, either alone or in combination with other radicals, denotes an amino group, substituted with two radicals that may be same or different selected from (C_1-C_6)alkyl, substituted alkyl, aryl, substituted aryl, or arylalkyl groups, such as dimethylamino, methylethylamino, diethylamino, phenylmethyl amino and the like and may be substituted.

The term "arylamino" used herein, either alone or in combination with other radicals, denotes an aryl group, as defined above, linked through amino having a free valence bond from the nitrogen atom, such as phenylamino, naphthylamino, N-methyl anilino and the like and may be substituted.

The term "aralkylamino" used herein, either alone or in combination with other radicals, denotes an arylalkyl group as defined above linked through amino having a free valence bond from the nitrogen atom e.g. benzylamino, phenethylamino, 3-phenylpropylamino, 1-napthylmethylamino, 2-(1-napthyl)ethylamino and the like and may be substituted.

The term "oxo" or "carbonyl" used herein, either alone (-C=O-) or in combination with other radicals, such as "alkylcarbonyl", denotes a carbonyl radical (–C=O-) substituted with an alkyl radical such as acyl or alkanoyl, as described above.

The term "carboxylic acid" used herein, alone or in combination with other radicals, denotes a –COOH group, and includes derivatives of carboxylic acid such as esters and amides. The term "ester" used herein, alone or in combination with other radicals, denotes –COO- group, and includes carboxylic acid derivatives, where the ester moieties are alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, and the like, which may be substituted; aryloxycarbonyl group such as phenoxycarbonyl, napthyloxycarbonyl, and the like, which may be substituted; aralkoxycarbonyl group such as benzyloxycarbonyl, phenethyloxycarbonyl, napthylmethoxycarbonyl, and the like, which may be substituted; heteroaryloxycarbonyl, heteroaralkoxycarbonyl, wherein the heteroaryl group, is as

defined above, which may be substituted; heterocyclyloxycarbonyl, where the heterocyclic group, is as defined earlier, which may be substituted.

The term "amide" used herein, alone or in combination with other radicals, represents an aminocarbonyl radical (H_2N-C=O-), wherein the amino group is mono- or di-substituted or unsubstituted, such as methylamide, dimethylamide, ethylamide, diethylamide, and the like. The term "aminocarbonyl" used herein, either alone or in combination with other radicals, along with other terms such as 'aminocarbonylalkyl", "n-alkylaminocarbonyl", "N-arylaminocarbonyl", "N,N-dialkylaminocarbonyl", "N-alkyl-N-arylaminocarbonyl", "N-alkyl-N-hydroxyaminocarbonyl", and "N-alkyl-N-hydroxyaminocarbonylalkyl", represents a carbonyl group attached to an amino group as defined earlier, which may be substituted. The terms "N-alkylaminocabonyl" and "N,N-dialkylaminocarbonyl" denotes aminocarbonyl radicals, as defined above, which have been substituted with one alkyl radical and with two alkyl radicals, respectively. Preferred are "lower alkylaminocarbonyl" having (C_1-C_6) lower alkyl radicals as described above attached to aminocarbonyl radical. The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote amiocarbonyl radicals substituted, respectively with one aryl radical, or one alkyl and one aryl radical. The term "aminocarbonylalkyl" includes alkyl radicals substituted with aminocarbonyl radicals.

The term "hydroxyalkyl" used herein, either alone or in combination with other radicals, denotes an alkyl group, as defined above, substituted with one or more hydroxy radicals, such as hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl and the like.

The term "aminoalkyl" used herein, alone or in combination with other radicals, denotes an amino (-NH_2) moiety attached to an alkyl radical, as defined above, which may be substituted, such as mono- and di-substituted aminoalkyl. The term "alkylamino" used herein, alone or in combination with other radicals, denotes an alkyl radical, as defined above, attached to an amino group, which may be substituted, such as mono- and di-substituted alkylamino.

The term "alkoxyalkyl" used herein, alone or in combination with other radicals, denotes an alkoxy group, as defined above, attached to an alkyl group, such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like. The term "aryloxyalkyl" used

herein, alone or in combination with other radicals, includes phenoxymethyl, napthyloxymethyl, and the like. The term "aralkoxyalkyl" used herein, alone or in combination with other radicals, includes $C_6H_5CH_2OCH_2$, $C_6H_5CH_2OCH_2CH_2$, and the like.

The term "alkylthio" used herein, either alone or in combination with other radicals, denotes a straight or branched or cyclic monovalent substituent comprising an alkyl group of one to twelve carbon atoms, as defined above, linked through a divalent sulfur atom having a free valence bond from the sulfur atom, such as methylthio, ethylthio, propylthio, butylthio, pentylthio and the like. Examples of cyclic alkylthio are cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio and the like, which may be substituted.

The term "thioalkyl" used herein, either alone or in combination with other radicals, denotes an alkyl group, as defined above, attached to a group of formula –SR', where R' represents hydrogen, alkyl or aryl group, e.g. thiomethyl, methylthiomethyl, phenylthiomethyl and the like, which may be substituted.

The term "arylthio' used herein, either alone or in combination with other radicals, denotes an aryl group, as defined above, linked through a divalent sulfur atom, having a free valence bond from the sulfur atom such as phenylthio, napthylthio and the like which may be substituted.

The term "alkoxycarbonylamino" used herein, alone or in combination with other radicals, denotes an alkoxycarbonyl group, as defined above, attached to an amino group, such as methoxycarbonylamino, ethoxycarbonylamino, and the like. The term "aryloxycarbonylamino" used herein, alone or in combination with other radicals, denotes an aryloxycarbonyl group, as defined above, attached to the amino group, such as C_6H_5OCONH, $C_6H_5OCONCH_3$, $C_6H_5OCONC_2H_5$, $C_6H_4(CH_3O)CONH$, $C_6H_4(OCH_3)OCONH$, and the like. The term "aralkoxycarbonylamino" used herein, alone or in combination with other radicals, denotes an aralkoxycarbonyl group, as defined above, attached to an amino group $C_6H_5CH_2OCONH$, $C_6H_5CH_2CH_2CH_2OCONH$, $C_6H_5CH_2OCONHCH_3$, $C_6H_5CH_2OCONC_2H_5$, $C_6H_4(CH_3)CH_2OCONH$, $C_6H_4(OCH_3)CH_2OCONH$, and the like.

The term "carbonylamino", "alkylaminocarbonylamino", "dialkylaminocarbonylamino" used herein, alone or in combination with other radicals, denotes a carbonylamino group (-$CONH_2$), attached to amino(NH_2) group, alkylamino group or dialkylamino group respectively, where alkyl group is as defined above.

The term "amidino" used herein, either alone or in combination with other radicals, denotes a –C(=NH)-NH_2 radical. The term "alkylamidino" denotes an alkyl radical, as discussed above, attached to an amidino group.

The term "guanidino" used herein, either alone or in combination with other radicals, denotes HN=C(NH_2)NH-, suitably substituted with other radicals, such as alkylguanidino, dialkylguanidino, where the alkyl group, as defined above is attached to a guanidino group, such as methylguanidino, ethylguanidino, dimethylguanidino, and the like.

The tem "hydrazino" used herein, either alone or in combination with other radicals, denotes –NHNH-, suitably substituted with other radicals, such as alkyl hydrazino, where an alkyl group, as defined above is attached to a hydrazino group.

The term "alkoxyamino" used herein, alone or in combination with other radicals, denotes an alkoxy group, as defined above, attached to an amino group. The term "hydroxyamino" used herein, alone or in combination with other radicals, denotes –NHOH moiety, and may be substituted.

The term "sulfenyl" or "sulfenyl and its derivatives" used herein, alone or in combination with other radicals, denotes a bivalent group, –SO- or RSO, where R is substituted or unsubstituted alkyl, aryl, heteroaryl, heterocyclyl, and the like.

The term "sulfonyl" or "sulfones and its derivatives" used herein, either alone or in combination with other radicals, with other terms such as alkylsulfonyl, denotes divalent radical –SO_2-, or RSO_2-, where R is substituted or unsubstituted groups selected from alkyl, aryl, heteroaryl, heterocyclyl, and the like. "Alkylsulfonyl" denotes alkyl radicals, as defined above, attached to a sulfonyl radical, such as methylsulfonyl, ethylsulfonyl, propylsulfonyl and the like. The term "arylsulfonyl" used herein, either alone or in combination with other radicals, denotes aryl radicals, as defined above, attached to a sulfonyl radical, such as phenylsulfonyl and the like.

The term alkylsulfonyloxy used herein, either alone or in combination with other radicals, denotes an alkylsulfonyl group as defined above attached to an oxygen atom.

The term alkylsulfonylamino used herein, either alone or in combination with other radicals, denotes an alkylsulfonyl group as defined above attached to a nitrogen radical.

The term "sulfonic acid or its derivatives", used herein, either alone or in combination with other radicals, denotes $-SO_3H$ group and its derivatives such as sulfonylamino(SO_2NH_2); N-alkylaminosulfonyl and N,N-dialkylaminosulfonyl radicals where the sulfonylamino group is substituted with one and two alkyl groups respectively, such as N-methylaminosulfonyl, N-ethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-methyl-N-ethylaminosulfonyl and the like; N-arylaminosulfonyl and N-alkyl-N-arylaminosulfonyl groups where the sulfonylamino group is substituted with one aryl radical, or one alkyl and one aryl radical; $-SO_3R$, wherein 'R' represents alkyl, aryl, aralkyl groups, as defined above, which may be substituted.

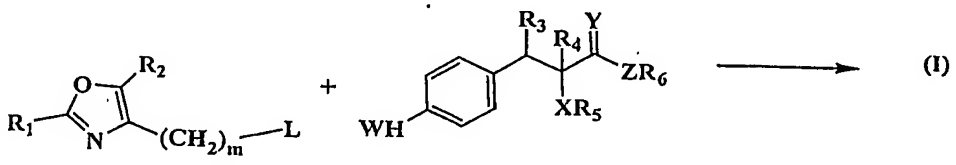
The term "phosphonic acid or its derivatives", used herein, either alone or in combination with other radicals, denotes $P(O)(OH)_2$, $P(O)(O(C_1\text{-}C_6)\ \text{alkyl})_2$, $P(O)(O\ \text{aryl})_2$, $P(O)(OH)(O(C_1\text{-}C_6)\text{alkyl})$, and the like.

The term "substituted" used in combination with other radicals, denotes suitable substituents on that radical such as substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted aryl, etc, mentioned anywhere in the specification. The suitable substituents include, but are not limited to the following radicals, alone or in combination with other radicals- hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, amidino, guanidino, hydrazino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocylyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylalkoxyalkyl, heterocyclylalkoxyacyl, acyl, acyloxy, acylamino, monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, aralkyloxycarbonylamino,

aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkoxyamino, hydroxyl amino, sulfenyl derivatives, sulfonyl derivatives, sulfonic acid and its derivatives, phosphonic acid and its derivatives.

The present invention also provides novel process for the preparation of compounds of formula (I) as well as intermediates involved in their synthesis. The compounds of the present invention can be prepared according to the general scheme provided below:

Scheme:



1a 1b

The reaction of compound of formula (1a), where all symbols are as defined earlier and L represents a leaving group such as halogen atom, *p*-toluenesulfonate, methanesulfonate, trifluoromethanesulfonate and the like with a compound of formula (1b) which may be optically active or racemic, where W is either O or S and all other symbols are as defined earlier, to produce a compound of general formula (I). This reaction may be carried out in the presence of solvents such as acetone, tetrahydrofuran, dimethylsulfoxide, dioxane, acetonitrile, dimethyl formamide, DME, benzene, toluene, pet. ether, heptane, hexane, 2-butanone, xylene, alcohols such as methanol, ethanol, propanol, butanol, iso-butanol, *tert*-butanol, pentanol and the like or a mixture thereof. Base such as alkali metal carbonate such as K_2CO_3, Na_2CO_3, $CsCO_3$, and the like; or alkali metal hydroxide such as NaOH, KOH and the like, may be used during this reaction. Alkali metal hydrides such as NaH, KH can be used whenever solvent employed is not protic or contain carbonyl group. The reaction may be carried out at a temperature in the range 0 °C to reflux temperature of the solvent(s) used and the reaction time may range from 1 to 48 hours.

i. The compounds of the present invention have asymmetric centers and occur either as racemates or racemic mixtures as well as individual stereoisomers, including optical

isomers, being included in the present invention The stereoisomers of the compounds of the present invention may be prepared by using (1b) in a single isomeric form.

ii. Mixture of stereoisomers may be resolved by conventional methods such as microbial resolution, resolving the diastereomeric salts formed with chiral acids or chiral bases. Chiral acids may be tartaric acid, mandelic acid, lactic acid, camphorsulfonic acid, amino acids and the like. Chiral bases may be cinchona alkaloids, (+) or (-) brucine, α-methyl benzylamine, (+) or (-) phenyl glycinol, ephedrine, amino sugars such as glucosamines or a basic amino acid such as lysine, arginine and the like.

iii. Resolution of the mixture of stereoisomers may also be effected by chemical methods by derivatization of the compound with a chiral compound such as chiral amines, chiral acids, chiral amino alcohols, amino acids into a 1:1 mixture of diastereomers and the diastereomers may be separated by conventional methods of fractional crystallization, chromatography and the like followed by cleaving the derivative (Jaques et al. "Enantiomers, Racemates and Resolution", Wiley Interscience, 1981; R. A. Sheldon, in "Chirotechnology", Marcel Dekker, Inc. NY, Basel, 1993, 173-204 and references therein; A. N. Collins, G. N. Sheldrack and J Crosby, in "Chirality in Industry II", John Wiley & Sons, Inc, 1997, 81-98 and references therein; E. L. Eliel and S. H. Wilen, in "Stereochemistry of Organic Compound", John Wiley & Sons, Inc, 1999, 297-464 and references therein.)

It will be appreciated that in any of the above mentioned reactions any reactive group in the substrate molecule may be protected, according to conventional chemical practice. Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. The methods of formation and removal in such protecting groups are those conventional methods appropriate to the molecule being protected. T. W. Greene and P. G. M. Wuts "Protective groups in Organic Synthesis", John Wiley & Sons, Inc, 1999, 3rd Ed., 201-245 along with references therein.

It will be appreciated that the above-mentioned preparation of the compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or pharmaceutically acceptable solvate thereof is a stereoselective procedure and that the compound of formula (I) is a single stereoisomer. Favorably, a compound of formula (I) is present in admixture with less than 50% w/w of its racemic isomer, suitably 80 - 100 % and

preferably 90 - 100 % pure, such as 90 - 95 %, most preferably 95 - 100 %, for example 95 %, 96 %, 97 %, 98 %, 99 % and 99.99 % optically pure.

Preferably the compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and/or pharmaceutically acceptable solvate thereof is in optically pure form.

The absolute stereochemistry of the compounds may be determined using conventional methods, such as X-ray crystallography.

The pharmaceutically acceptable salts forming a part of this invention may be prepared by treating the compound of formula (I) with 1-6 equivalents of a base such as sodium hydride, sodium methoxide, sodium ethoxide, sodium hydroxide, potassium tert-butoxide, calcium hydroxide, calcium acetate, calcium chloride, magnesium hydroxide, magnesium chloride, magnesium alkoxide and the like. Solvents such as water, acetone, ether, THF, methanol, ethanol, t-butanol, 2-butanone, dioxane, propanol, butanol, isopropanol, di*iso*propyl ether, *tert*-butyl ether or mixtures thereof may be used. Organic bases such as lysine, arginine, methyl benzylamine, ethanolamine, diethanolamine, tromethamine, choline, guanidine and their derivatives may be used. Acid addition salts, wherever applicable may be prepared by treatment with acids such as tartaric acid, mandelic acid, fumaric acid, malic acid, lactic acid, maleic acid, salicylic acid, citric acid, ascorbic acid, benzene sulfonic acid, p-toluene sulfonic acid, hydroxynaphthoic acid, methane sulfonic acid, acetic acid, benzoic acid, succinic acid, palmitic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and the like in solvents such as water, alcohols, ethers, ethyl acetate, dioxane, THF, acetonitrile, DMF or a lower alkyl ketone such as acetone, or mixtures thereof.

Another aspect of the present invention comprises a pharmaceutical composition, containing at least one of the compounds of the general formula (I), their derivatives, their analogs, their tautomeric forms, their pharmaceutically acceptable salts as an active ingredient, together with pharmaceutically employed carriers diluents and the like.

Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington: the Science and Practice of Pharmacy, 19th Ed., 1995. The compositions may be in the conventional forms, such as capsules, tablets, powders, solutions, suspensions, syrups, aerosols or topical applications. They may contain suitable solid or liquid carriers or in suitable

sterile media to form injectable solutions or suspensions. The compositions may contain 0.5 to 20 %, preferably 0.5 to 10 % by weight of the active compound, the remaining being pharmaceutically acceptable carriers, excipients, diluents, solvents and the like.

Typical compositions containing a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipients which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material, which acts as a vehicle, excipients or medium for the active compound. The active compound can be absorbed on a granular solid container for example in a sachet. Some of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium sterate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acids monoglycerides and diglycerides, pentaerythritol fatty acids esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preservatives, sweetening agents or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active drug to the appropriate or desired site of action effectively, such as oral, nasal, transdermal, pulmonary or parental e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, preferably through oral route.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound of formula (I) dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agent, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabens.

For parental application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablet, dragees or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferably, carriers for tablets, dragees or capsules include lactose, corn starch and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tabletting techniques may contain:

Core:

Active ingredient (as free compound or salt thereof)	100 g
Wheat starch	45 g
Maize starch	55 g
Microcrystalline cellulose	12 g
Ethyl cellulose	8 g
Magnesium stearate	5 g

The coating may compose of the following ingredients in varying compositions

Lac
Gelatin
Gum arabic
Sucrose
Titanium dioxide
Beeswax
Carnauba wax
Ethyl vanilin

The compounds of general formula (I) or the compositions thereof are useful for the treatment and/or prophylaxis of disease caused by metabolic disorders such as hyperlipidemia, insulin resistance, leptin resistance, hyperglycemia, obesity, or inflammation.

These compounds are useful for the treatment of hypercholesteremia, familial hypercholesteremia, hypertriglyceridemia, type 2 diabetes, dyslipidemia, disorders related to syndrome X such as hypertension, obesity, insulin resistance, coronary heart disease, atherosclerosis, xanthoma, stroke, peripheral vascular diseases and related disorders, diabetic complications, certain renal diseases such as glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, psoriasis, polycystic ovarian syndrome, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, arteriosclerosis, xanthoma, pancreatitis and for the treatment of cancer.

The compounds of the invention may be administered to a mammal, especially, a human in need of such treatment, prevention, elimination, alleviation or amelioration of diseases mentioned above.

The compounds of the present invention are effective over a wide dosage range, however, the exact dosage, mode of administration and form of composition depends upon the subject to be treated and is determined by the physician or veterinarian responsible for treating the subject. Generally, dosages from about 0.025 to about 200 mg preferably from about 0.1 to about 100 mg, per day in single or multiple dosage spread throughout the day may be used. Generally, the unit dosage form comprises about 0.01 to 100 mg of the compound of formula (I), as an active ingredient together with a pharmaceutically acceptable carrier. Usually suitable dosage forms for nasal, oral, transdermal or pulmonary administration comprises from about 0.001 mg to about 100 mg, preferably from 0.01 mg to about 50 mg of the active ingredient mixed with a pharmaceutically acceptable carrier or diluent.

In another aspect of the present invention, method of treatment and/or prevention of the diseases mentioned above by treatment with compounds of the present invention are provided.

In a further aspect of the present invention, use of one or more compounds of the general formula (I) or pharmaceutically acceptable salts, for the preparation of a medicament thereof for the treatment and/or prevention of diseases mentioned in this document is provided.

In still further aspect of the present invention use of the compounds of the present invention alone or in combination with statins, glitazones, biguanides, angiotensin II inhibitors, aspirin, insulin secretagogue, β-sitosterol inhibitor, sulfonylureas, insulin, fibric acid derivatives, nicotinic acid, cholestyramine, cholestipol or probucol, α-glycosidase inhibitors or antioxidants, which may be administered together or within such a period as to act synergistically together.

Dated this 11th day of August 2003

Signature _____

Dr. Braj Bhushan Lohray (President, Zydus Research Centre)
For Cadila Healthcare Limited

To
The Patent Office
at, Mumbai